REMARKS

As a preliminary matter, Applicant gratefully acknowledges the Examiner's thorough review of Applicant's Appeal Brief filed on May 18, 2005 and withdrawal of the final rejection of the previous Office Action. Also, Applicant acknowledges the Examiner's withdrawal of the previous art rejections under 35 U.S.C. § 103(a).

Additionally, Applicant appreciates the courtesies extended by Examiner Borin during the Telephonic Interviews of August 15, 2005 and November 7, 2005. During the August interview, Examiner Borin suggested several claim amendments that would place the application in condition for allowance. Furthermore, the Examiner requested that Applicant submit, further to the personal interview of October 15, 2004, additional evidence via the enclosed inventor Declaration Under 37 C.F.R. § 1.132 (the "Schwartz Declaration") showing that administration of an effective dose of HGF causes a reduction of inflammation in the intestine by reducing the gene expression of the inflammatory cytokine mediators.

By this Amendment, claims 1-33 are cancelled without prejudice and disclaimer and new claims 34-43 have been added. Thus, claims 34-43 are currently pending in this application. During the November 7, 2005 Telephonic Interview, the Examiner agreed that new claims 34-43 submitted herewith would be allowable. In particular, independent claim 34 recites that administration of "HGF reduces lesions of the intestine and reduces the gene expression of cytokine inflammatory mediators." Support for newly added claims 34-43 may be found in the originally filed claims and throughout the specification. These claims are allowable because the prior art fails to disclose or suggest at least these features as discussed immediately below.

Accordingly, Applicant respectfully requests reconsideration, timely withdrawal of the pending rejections, and allowance of the application.

Traversal of Rejections Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 7, 9-12, and 21-33 under 35 U.S.C. § 103(a) as being "obvious over Bozkurt et al (J Clin Ultrasound. 1994 Feb;22(2):85-91) in view of Dignass et al (and Nasrat et al (Journal of Clinical Investigation, 9395), 2056-2065, 1994)." Office Action at page 2. Applicant respectfully traverses this rejection for at least the following reasons.

The Examiner has failed to establish a *prima facie* case of obviousness because none of these references whether taken singly or in combination, disclose or suggest each and every limitation of the claimed invention nor do the references provide any suggestion or motivation to combine the teachings of the Nusrat reference with the Dignass reference to arrive at the claimed invention.

Bozkurt is cited for disclosing "that patients having inflammatory bowel disease suffer from pathological lesions of intestine." *Id.* at 2. The Bozkurt reference is deficient as a primary reference because it fails to disclose or suggest each and every element of the claimed invention. Specifically, for example, nowhere does the primary reference disclose or suggest "reducing the gene expression of cytokine inflammatory mediators" by administering an effective dose of HGF as recited in independent claim 34.

Next, the secondary and tertiary references cited by the Examiner are only directed to the proliferation of intestinal epithelial cells in *in vitro* cell culture systems. In particular, Dignass et

al., the Examiner's secondary reference, is directed to intestinal cell proliferation and motility using *in vitro* systems, and Nusrat et al., the Examiner's tertiary reference, is directed to intestinal restitution (wound resealing). Therefore, like the Bozkurt reference, nowhere do the Dignass or Nusrat references disclose or suggest "reducing the gene expression of cytokine inflammatory mediators" by administering an effective dose of HGF as recited in independent claim 34. Indeed, the Examiner is still assuming that the only primary mechanism by which HGF is effective in inflammatory bowel disease is through cellular proliferation. In other words, the claimed invention not only includes reducing lesions in the patient but also includes reducing intestinal inflammation in the patient as shown by the unexpected results in the Schwartz Declaration filed concurrently herewith. Thus, even if the references were combined as suggested by the Examiner, they do not result in the claimed invention.

Furthermore, the required motivation or suggestion to combine the references as suggested by the Examiner is missing, so the proposed combination would not have been obvious. The Examiner attempts to supply the requisite motivation by arguing that

> it would have been *prima facie* obvious to one skilled in the art...to reduce pathological lesions (i.e. wounds) in patients suffering from inflammatory bowel disease. It would be obvious to an artisan, therefore, to be motivated to treat patients suffering from inflammatory bowel disease with HGF because both Nusrat and Dignass demonstrate that HGF stimulates two essential intestinal epithelial cell functions, proliferation and restitution, which would result in wound restitution and because both references suggest that HGF would be useful *in vivo* to repair intestinal epithelial erosions/ulcerations. *Id.* at 3-4.

Since neither the Dignass nor Nusrat references, as discussed above, disclose or suggest reducing the gene expression of cytokine inflammatory mediators, one skilled in the art would not have found any reason to combine the teaching of Dignass with Nusrat as alleged by the Examiner. One simply cannot arrive at the claimed reducing step (i.e., reducing the gene expression of cytokine inflammatory mediators) of the claimed invention employing the disclosure of these prior art references. Therefore, there is no motivation to combine these references, and even if they were combined, the claimed reducing step is still missing.

Next, the Examiner maintains the allegation that although the references do not expressly state the claimed HGF dosages the concentration of dosage ranges of HGF is within the skill of the ordinary worker as a part of the process of normal optimization. *Id.* at 4. None of the art references cited by the Examiner disclose or suggest the effective HGF dosage range of the invention. The references cited by the Examiner only provide HGF dosage ranges applicable to *in vitro* cell culture studies. The dose of HGF used in *in vitro* cell culture studies cannot be simply extrapolated by one skilled in the art to arrive at the effective HGF dosage ranges to be administered to a patient. Therefore, the Applicant respectfully submits that the claims of this application patentably distinguish over the prior art relied upon by the Examiner.

The Schwartz Declaration

The Examiner has requested the inventor, Dr. Schwartz further to the personal interview of October 15, 2004, where Dr. Schwartz clearly demonstrated the surprising anti-inflammatory capabilities of HGF treatment in patients afflicted with IBD, submit this evidence via a Rule 132

Declaration. Therefore, concurrently filed herewith is the Schwartz Declaration. The Examiner indicated in the November 7, 2005 Telephonic Interview that the Schwartz Declaration, previously provided as a draft, would be acceptable.

In the Schwartz Declaration, Dr. Schwartz has submitted evidence clearly demonstrating that HGF possesses an unexpected and superior degree of effectiveness, compared to Nusrat and Dignass (and the other prior art of record), which only show that HGF facilitates ***cell proliferation*** of epithelial intestinal cells in *in vitro* cell culture systems. Indeed, Dr. Schwartz has demonstrated the unexpected and superior results that an effective dose of HGF administered to a patient afflicted with IBD reduced inflammation of the intestine as evidenced by gross analysis of the bowel and by a reduction in both protein and gene expression of the inflammatory mediators.

Referring to the Schwartz Declaration, Dr. Schwartz demonstrated the unexpected results that HGF treatment of rats afflicted with IBD (i.e., HLA-B27 transfected rats) resulted in a ***statistically significant decrease*** in protein expression of two inflammatory cytokines, tumor necrosis factor-α (TNF- α) and interferon-γ (IFN- γ) in HGF-treated HLA-B27 rats compared to untreated HLA-B27 rats. *See* Exhibits 5 and 6 of the Schwartz Declaration, respectively. (¶ 8). Furthermore, Dr. Schwartz also performed semi-quantitative reverse transcription polymerase chain reaction (RT-PCR) and demonstrated that HGF decreased the RNA expression of TNF- α and IFN- γ. (*Id.*) These unexpected findings, which are not disclosed or suggested by the cited references (or any other prior art of record), clearly demonstrate that HGF has a direct or indirect effect on these inflammatory mediators. (*Id.*) Thus, these findings demonstrate that the

mechanism of action for the clearly demonstrated benefit of HGF treatment in this model of IBD is its anti-inflammatory capability by blocking the effects on the mucosa of inflammatory mediators rather than accelerating the proliferation of intestinal mucosa, as disclosed by the cited art of record, and replace the damaged and inflamed intestine. (*Id.*)

Extension of Time

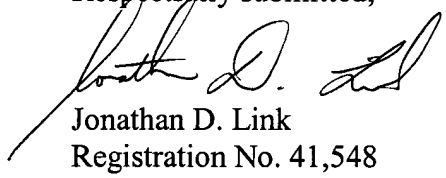
A Petition for a one (1)-month extension of time under 37 C.F.R. § 1.136(a) and accompanying fee in the amount of $ 60.00 is filed herewith extending the period for responding to the outstanding office action. Applicant believes that no further extensions of time are required other than those in the accompanying Petition. If extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned for under 37 C.F.R. § 1.136(a). Any fees required for further extensions of time and any fees for the net addition of claims are hereby authorized to be charged to our Deposit Account No. 23-1951.

CONCLUSION

Applicant submits that a full and complete response has been made to the pending Office Action and respectfully submits that all of the stated grounds for rejection have been overcome or rendered moot. Accordingly, Applicant respectfully submits that all pending claims are patentably distinct from the prior art of record and are in condition for allowance. The Examiner is thus respectfully requested to promptly pass the above application to issue.

In light of the protracted prosecution of this application, should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is requested to contact the Applicant's undersigned representative at the number below to expedite prosecution. Prompt and favorable consideration of this Reply is respectfully requested. Applicant respectfully requests that a timely Notice of Allowance be issued for this application.

Respectfully submitted,



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